UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/423,554	11/10/1999	ARISTOS ARISTIDOU	0933-148P	6884

7590 05/06/2003

BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 220400747

EXAMINER	
WALICKA, MALGORZATA A	

ART UNIT	PAPER NUMBER
1652	19

DATE MAILED: 05/06/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/423,554	ARISTIDOU ET AL.	
	Examin r	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2003 and 14 February 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *11-16,23,24,27,31,32 and 34-37* is/are withdrawn from consideration.

5)☒ Claim(s) *25 and 26* is/are allowed.

6)☒ Claim(s) *1-1, 17-22, 28-30, 33, 38-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

The Reply under 37 CFR § 1.111, filed on January 16, 2003 as paper No. 17 and Supplemental Reply field on February 14, 2003 as paper No. 18 are acknowledged. Amendments to the claims have been entered as requested. Claims 1-8, 17, 19, 21, 28 and 39 are amended; new claims 40 and 41 are added. Claims 1-41 are pending; claims 1-10, 17-22, 25, 26, 28-30, 33, 38 and 39-41 are the subject of this Office Action. Claims 11-16, 23-24, 27, 31-32 and 34-37 are withdrawn from consideration as drawn to the non-elected invention.

Detailed Office Action

Declaration under 37 CFR section 1.132.

On page 8 of their response Applicants write, "Attached to this reply, please find a declaration executed under the provisions of 37 CFR section 1.132 wherein one of the inventors swears to the public availability of the genes described in the instant invention".

The declaration is not attached to the replay.

1. Objections

1.1. Specification

The disclosure is still objected to for the reasons stated in the previous Office Action, paper No. 15. The specification contains an embedded hyperlink and/or other form of browser-executable code; see page 47, line 7 and 30. Applicant is required to

delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The specification is still objected to because it misses a list of transformed organisms together with genes used for transformation including genes that are comprised in transformants extrachromosomally, in plasmid, and integrated into the genome. The list should also contain the source and/or nucleotide sequence of the genes used to obtain transformants.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicants' cooperation is requested in correcting any errors of which applicant may become aware.

Claim 21 is objected to as being dependent on claim 9. The claim depends on claim 19.

Version of claims amended and with markings to show changes made filed on January 2003 as paper No. 17 is different than the list of all the pending claims which are ready for further action on the merits. The latter was filed on Feb. 14, 2003 as paper NO. 18/19 and examined.

2.1. 35 USC 112, second paragraph

2.1.1. Rejections withdrawn

Claim 1

The examiner acknowledges substituting in claim 1 the improper term "pyridine nucleotide" by the correct "nicotinamide adenine dinucleotide or nicotinamide adenine

dinucleotide phosphate", both in oxidized and reduced forms, i.e., NAD/NADH and NADP/NADPH.

Claim 3

The rejection of claim 3 for indefinite phrase "producing a product faster" made in paper No. 15 is withdrawn in the light of applicants' arguments.

Claim 4

The rejection of claim 4, made in paper 15, for indefinite phrase "less CO_2" is withdrawn in the light of Applicants' arguments.

Claim 5

The rejection of claim 5, made in paper 15, for the indefinite phrase "reduced oxygen requirement per unit of a product produced" is withdrawn in the light of Applicants' arguments.

Claim 6 and 7

Rejection of claim 6 and 7, made in paper 15, for the indefinite phrase "conditions of a biotechnological process" is withdrawn because the claims have been amended.

2.1.2 Rejections not withdrawn

Claims 1-10, 17- 22, 28-30, 33, 38 and 39-41 are rejected under 35 U.S.C. 112, for the reasons indicate in the previous Office Actions, papers No. 10 and 13 and 15.

Claim 1, 2 and 40

The term "functional coupling" in the phrase "functional coupling of the oxidation and reduction" of claim 1, 2 and 40 is unclear. It seems that in a living cells the oxidation and reduction processes are coupled. The Applicants write on page 9, line 31 of the specification: "the present invention provides a microorganism which is transformed with at least one recombinant DNA molecule encoding or otherwise causing the expression of at least one of the pair of dehydrogenases with opposite coenzyme specificities for NAD/NADH and NADP/NADPH, but at least one common substrate." It is unclear whether by "functional coupling" Applicants mean "expression of at least one of the pair of dehydrogenases with opposite coenzyme specificities for NAD/NADH and NADP/NADPH". If a cell expresses an endogenous dehydrogenase using NADP, transforming said cell with one exogenous dehydrogenase that uses NAD will cause the coupling. Otherwise, one has to transform the cell with a pair of dehydrogenases, one of which that uses NAD, the other NADP.

In their current response, paper No. 17, Applicant write,

"Applicants assert that this term [functional coupling of the oxidation and reduction, MW] would readily be

understood by one of skill in the art when read in the light of the specification. This term is explained at page 10, line 4 *et seq*. Accordingly, Applicants assert that there is nothing vague or indefinite about this term."

Applicants' arguments have been fully considered but they are found not persuasive. On page 10 line 4 one reads: "This results in a functional coupling of the dehydrogenases catalyzing reactions (1) and (2). It is not a necessary part of the invention, but neither is it excluded, that the two dehydrogenases should physically associate within the transformed cell. The functional coupling allows the following reactions to occur, which tend to equilibrate the NAD/NADH and NADP/NADPH coenzyme couples..." Thus Applicants write here about results of functional coupling. Moreover the phrase 'to equilibrate the NAD/NADH and NADP/NADPH coenzyme couples' is vague, because in any living cell NAD/NADH and NADP/NADPH coenzyme couples are in the equilibrium that is characteristic for that very cell.

suggest more efficiently than not transformed cell

The term "more efficiently" in claim 1 and 2 is a relative terms which render the claim indefinite. The term "more efficiently" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Opposite to what Applicants write on page 9 of their response, paper No. 17, the term "more efficiently" is not deleted from claim 1.

The amended claim 2 is rejected for the relative phrase "expression under different physiological conditions." The phrase is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The phrase is indefinite, because it is unknown in relation to what conditions the expression conditions used in the invention are different.

The amendment to claim 1 and 2 introduces such limitations as producing in a cheaper process, higher specific rate, higher yield of product form carbohydrate, smaller amounts unwanted side products, and a smaller oxygen requirement. These are relative phrases, which render the claims indefinite. The phrases " cheaper process", "higher specific rate", "a higher volumetric rate", "higher yield of product form carbohydrate", "smaller amounts unwanted side products, and "a smaller oxygen requirement " are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The phrases are indefinite, because it is unknown in relation to what the producing is cheaper, specific rate is higher or the yield is higher.

In addition, these limitations are limitations of the use of product claimed by claim 1. They do not provide specific characteristics of the claimed transformant *per se,* because there are many transformants, which when used make the process of use

cheaper than when other transformants, nontransformed microorganisms or other microorganisms are used for the same process.

Claim 40 is indefinite because it recites the phrase "one or more products" which is indefinite.

Dependent claims 3-10, 18-20, 22, 28-30, 33 and 38-39 and 41 are including into this rejection because they do not correct deficiency of the claim from which they depend.

2.2. 35 USC 112, first paragraph

2.2.1. Lack of written description

Claims 2-10, 17- 22, 28-30, 33, 38-39 and new claims 40-41 are rejected for reasons stated in the previous Office Actions No. No. 10 and 13 and 15 and reiterated herein.

The claims are directed to a microorganism transformed with at least one recombinant DNA molecule causing the expression of a gene of at least one enzyme that causes the coupling the oxidation and reduction of substrates by two dehydrogenase reactions. The claims are directed to the large genus of microorganisms transformed with a DNA molecule that is from any natural source, as well as artificial. The disclosure fails to teach such microorganism and such DNA molecules. Applicants only mention, without identifying nucleotide sequences, promoters such as PGK or ADH causing expression of constitute NAD-dependent

glutamate dehydrogenase in *S. cerevisiae* (page 26, line 11). However, Applicant do not disclose any *S. cerevisiae* transformant comprising said promoters nor guide how to perform *in vivo* recombination so that these promoters were incorporated in the proper place of the *S. cerevisiae* genome. Furthermore, those skilled in the art are aware that promoters suitable for glutamate dehydrogenase in *S. cerevisiae* are not suitable for other genes encoding enzymes useful in making the claimed invention, as well as for other microorganisms to be transformed. Thus, because Applicant do not teach any microorganism that has expression of ~~a~~ the gene of interest enhanced by any species of the large genus of the promoter DNA molecules, one skilled in the art is not convinced that the inventors, at the time the application was filled, had possession of the claimed invention.

Claims 1, 3-10, 17- 22, 28-30, 33, 38-39 and new claim 41 are rejected for lack of written description of "recombinant DNA molecule encoding at least part of an enzyme that causes the functional coupling". The claims are directed to a large and variable genus of DNA molecules for which structural description is completely lacking in the specification or claims, because no sequence identification, for protein or DNA, is provided.

The representative species of the genus are NAD–dependent glutamate dehydrogenase and xylulokinase from *S. cerevisiae*, or xylose reductase and xylitol reductase from *Pichia stipis.* The specification is silent about the structure of protein or DNA of representative species and the structure/function relationship for the

[redacted]

representative species. Thus, the fragments of representative enzymes that may cause functional coupling are not identified even in case of representative species. The specification fails to teach identifying characteristics of the claimed genus of enzymes, their fragments and encoding DNA molecules. The disclosure does not provide sufficient description to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Thus, predictability of the function of the claimed genus is not apparent.

Federal Circuit states that the primary function of the written description requirement is to insure that an inventor had possession of the claimed subject matter and to allow one skilled in the art to recognize what is claimed. *See in re Blaser*, 556F.2d 534, 194 U.S. P. Q. 122(CCPA 1977), *Enzo Biochem*, 285 F. 3d 1013, 62 U.S.P.Q.2d 1289. "The written description requirement is satisfied by the disclosure of the claimed subject matter in such a descriptive means, *e.g.*, words, structures, figures and diagrams, to allow one skilled in the art to visualize or recognize the claimed subject matter, *Enzo Biochem.* 285 F. 3d 1013."

One skilled in the art is not able to visualize or recognize the invention because the claimed subject matter is not disclosed in such descriptive means as structures, or figures presenting such structures or even words presenting details of structures.

Given the lack of structural characteristics of additional representative species as encompassed by the claim, Applicants have failed to sufficiently describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would

recognize Applicants were in possession of the claimed invention when the application was filed.

The amendment to claim 1 introduces such limitations as producing in "a cheaper process", at "higher specific rate", "higher yield of product form carbohydrate", with "a smaller amounts unwanted side products". These limitations are lacking written description. The specification does not set forth any calculation of the cost of production of any chemical compound using the transformant of claim 1 nor the specification does compare said costs with those for other microorganisms used for production of the same compound.

The term "unwanted side product" is a generic term, which comprises a large and variable genus of side products that are synthesized during fermentation of microorganism. Applicants describe only one species of said genus, i.e., CO_2. This is however insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Applicants have failed to sufficiently describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention when the application was filed.

The amendment to claim 2 and necessitates rejection of claim 2 and dependent claims for lack of written description of NAD/NADH- or NADP/NADPH- linked dehydrogenases. The claim is directed to a large and variable genus of NAD/NADH- or

NADP/NADPH- linked dehydrogenases that share a common substrate and have different specificities for the NAD/NADH or NADP/NADPH coenzyme couples. The scope of the genus covers dehydrogenases from any biologic and man-made source. The representative species of the genus are NAD–dependent glutamate dehydrogenase and xylulokinase from *S. cerevisiae*, or xylose reductase and xylitol reductase from *Pichia stipis.* The specification is silent about the structure of protein or encoding DNA of representative species and the structure/function relationship for the representative species, thus the charcteristic structural feature of the genus is unknown. The specification fails to teach identifying characteristics of the claimed genus of enzymes and encoding DNA molecules. The disclosure does not provide sufficient description to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Thus, predictability of the function of the claimed genus is not apparent.

Federal Circuit states that the primary function of the written description requirement is to insure that an inventor had possession of the claimed subject matter and to allow one skilled in the art to recognize what is claimed. *See in re Blaser*, 556F.2d 534, 194 U.S. P. Q. 122(CCPA 1977), *Enzo Biochem*, 285 F. 3d 1013, 62 U.S.P.Q.2d 1289. "The written description requirement is satisfied by the disclosure of the claimed subject matter in such a descriptive means, *e.g.*, words, structures, figures and diagrams, to allow one skilled in the art to visualize or recognize the claimed subject matter, *Enzo Biochem.* 285 F. 3d 1013."

[redacted]

One skilled in the art is not able to visualize or recognize the invention because the claimed subject matter is not disclosed in such descriptive means as structures, or figures presenting such structures or even words presenting details of structures.

Given the lack of structural characteristics of representative species as encompassed by the claim, Applicants have failed to sufficiently describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention when the application was filed.

The amendment to claim 2 necessitates rejection of claims 2-10, 17- 22, 28-30, 33, 38-39 and new claim 41 for lack of written description of a DNA molecule that replaces the natural promoter of a host cell gene encoding a NAD/NADH- or NADP/NADPH –linked dehydrogenase. The claim is directed to a large and variable genus of DNA molecules that have the promoter function. As indicate in the previous Office Action, paper No. 15, the only representative species mentioned by Applicants, without identifying nucleotide sequences, are promoters such as PGK or ADH causing expression of constitute NAD-dependent glutamate dehydrogenase in *S. cerevisiae* (page 26, line 11). The specification is silent about the structure of representative species, thus the charcteristic structural feature of the genus is unknown. The specification fails to teach other identifying characteristics of the claimed genus of DNA molecules. The disclosure does not provide sufficient description to put one of skill in

[redacted]

the art in possession of the attributes and features of all species within the claimed genus. Thus, predictability of the function of the claimed genus is not apparent.

Federal Circuit states that the primary function of the written description requirement is to insure that an inventor had possession of the claimed subject matter and to allow one skilled in the art to recognize what is claimed. *See in re Blaser*, 556F.2d 534, 194 U.S. P. Q. 122(CCPA 1977), *Enzo Biochem*, 285 F. 3d 1013, 62 U.S.P.Q.2d 1289. The written description requirement is satisfied by the disclosure of the claimed subject matter in such a descriptive means, *e.g.*, words, structures, figures and diagrams, to allow one skilled in the art to visualize or recognize the claimed subject matter, *Enzo Biochem*. 285 F. 3d 1013."

One skilled in the art is not able to visualize or recognize the invention because the claimed subject matter is not disclosed in such descriptive means as structures, or figures presenting such structures or even words presenting details of structures.

Given the lack of structural characteristics of representative species as encompassed by the claim, Applicants have failed to sufficiently describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention when the application was filed.

In addition to lack of written description of promoters, Applicant do not disclose any *S. cerevisiae* or other microorganisms transformants comprising said promoters nor guide how to perform *in vivo* recombination so that these promoters were incorporated in the proper place of the *S. cerevisiae* genome. Furthermore, those skilled in the art

are aware that promoters suitable for glutamate dehydrogenase in *S. cerevisiae* are not suitable for other genes encoding enzymes useful in making the claimed invention, as well as for other microorganisms to be transformed. Thus, because Applicant do not teach any microorganism that has expression of a gene of interest enhanced by any of the large species of the promoters, the one skilled in the art is not convinced that the inventors, at the time the application was filled, had possession of the claimed invention.

Claims 1-10, 17-22 28-30, 33, 38-39 and 41 are rejected under 35 USC 112, first paragraphs, as directed to microorganism producing from carbohydrates a product more reduced than pyruvate. The claims are directed to a large and versatile genus of chemical compounds for which identifying characteristics is lacking in the disclosure. The representative species are ethanol, xylitol, lysine and polyhydroxybutyrate and lysine. This is however not sufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Thus, predictability of the function of the claimed genus is not apparent.

Federal Circuit states that the primary function of the written description requirement is to insure that an inventor had possession of the claimed subject matter and to allow one skilled in the art to recognize what is claimed. *See in re Blaser*, 556F.2d 534, 194 U.S. P. Q. 122(CCPA 1977), *Enzo Biochem*, 285 F. 3d 1013, 62 U.S.P.Q.2d 1289. The written description requirement is satisfied by the disclosure of the claimed subject matter in such a descriptive means, *e.g.*, words, structures, figures

and diagrams, to allow one skilled in the art to visualize or recognize the claimed subject matter, *Enzo Biochem.* 285 F. 3d 1013."

One skilled in the art is not able to visualize or recognize the invention because the claimed subject matter is not disclosed in such descriptive means as structures, or figures presenting such structures or even words presenting details of structures.

In their response Applicants write how to calculate the reductance and define whether the compound is more reduced than pyruvate; see page 10 line 3 of the response, paper No. 17. This, however, does not change the fact that not all compounds that are more reduced than pyruvate where shown to be produced by the disclosed transformants.

In conclusion, given the lack of structural characteristics of representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention when the application was filed.

2.2.3. Remarks and conclusions

In their Response, paper No. 17, in the section *Written Description,* page 12, Applicants write,

"Applicants assert that **full possession** of the claimed invention was had at the time of filling the application

and that the claimed invention **can be practiced to its full scope** without undue experimentation [emphasis added]."

The Applicant assertion has been fully considered but is found not persuasive because of the above rejections for lack of written description, and rejections for lack of enablement, and scope of enablement that follow.

In addition to this assertion Applicants argument are as follows:

"Applicants, in written description, have shown an increase in xylitol production (please see Example 8, on page 34, line 26 and Fig. 4) and lysine production (Example 23, Table 4 on page 52) in addition to that of ethanol. Applicants are claiming a general method that improves the method of making such products" (page 12 line 15), and

"Example 24 teaches how to use the invention further to increase production of polyhydroxybutyrates by genetically engineered *S. cerevisiae*" (page 13, line 11).

Applicant's arguments have been fully considered but are found not persuasive for the following reasons. The rejected claims are the claims directed to transformants described in terms of general concept. This concept was reduced into practice only in case of transfomants of yeasts and *Corynebacterium*; see page 55 of the specification. Of the transformants on page 55 only transformants of S. *cerevisiae and pombe* were deposited in the DSMZ-Deutsche Sammlungen von Mikroorganismen und Zellkulturen

GmbH and will be publically available when the patent on this application is issued. For that reason, in the first Office Action (paper No.10) claims 25 and 26 were said to be allowable and were allowed in the next Office Actions, paper No. 13 and 15.

Applicants attention is turned to the fact that claims directed to the method of production of ethanol (the elected species of products) have been rejected because they are dependent on the rejected claims directed to a concept and not to real transformants possessed by Applicants at the time the invention was filed. The method of production of ethanol by the yeast transformants of claim 25 and 26 is fully described and enabled. Production of xylitol by transformants of claim 25 and 36 and production of polyhydroxybutyrates by genetically engineered *S. cerevisiae* is also described, similarly production of lysine by transformed *Corynebactrium*; Example 23, Table 4.

2.2.4. Lack of enablement

Claim 2-10, 17- 22, 28-30, 33, 38, 39 and 41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The amendment of claim 2 did not put the claims in the conditions for allowance.

The claims are directed to a microorganism transformed with a DNA molecule that replaces the natural promoter of a host cell gene encoding a NAD/NADH- or NADP/NADPH –linked dehydrogenase by another promoter that:

(1) causes stronger expression or

[redacted]

(2) expression under different physiological conditions than said natural promoter.

To make such transformed microorganism one skilled in the art has to know promoter sequences of the genes of interest as well as said different physiological conditions under which the expression is going to take place. Without a guidance on the part Applicant as to the sequence of promoter used for replacement, as to the physiological conditions other than those suitable for natural promoter and how to obtain said transformants, i.e., how to replace the natural promoter, making and using the invention involves undue experimentation. Factors to be considered in determining whether undue experimentation is required, are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses any microorganism transformed with any promoter from any organism or man-made, that increases expression of a gene encoding a NAD/NADH- or NADP/NADPH –linked dehydrogenase, or increases this expression of said dehydrogenase under different physiological conditions than that suitable for the natural promoter. Although the art of causing or increasing gene expression by transforming microorganism is pretty well developed, and skills of those in the art advanced, the predictability of the results is low

without knowing the microorganism, the particular gene to be expressed and a suitable promoter to replaced the natural promoter, these, however, are not sufficiently described (see the above rejection for lack of written description). In addition, Applicants fail to give examples of different physiological conditions than that suitable for said natural promoter. Thus, one skilled in the art is left with finding the conditions suitable for increasing expression of any dehydrogenase under control of any promoter wherein these conditions are proper for growth of transformed microorganism. Because Applicants do not provide any guidance as to how to replace promoters, or what are different physiological conditions, Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims.

Without further guidance on the part of applicants as to which DNA molecule to use for induction or increase in expression of particular gene and what conditions are considered different physiological conditions in particular microorganism, results are unpredictable and probability of success very low. Thus without the further guidance, the experimentation left to those skilled in the art is improperly undue.

2.2.5. Scope of enablement

1-10, 17-22 28-30, 33, 38-39 and 41 remain rejected for reasons indicated in the previous Office Action, paper 13, because the claims are directed to production from carbohydrates any chemical that is more reduced than pyruvate, whereas the disclosure provide enablement for production ethanol, xylitol, lysine and polyhydroxybutyrates.

[redacted]

2.2.63. Remarks

In their response to rejection for lack of enablement Applicants write, paper No.17, page 14, line 29, write, "The principles of replacing a specific DNA sequence in a host organism by a new specific sequence by homologous recombination is very well known." and further, "REMI (restriction enzyme mediated integration) is a well established method. Since early 1990's REMI has been practiced without undue experimentation."

Applicants' argument has been fully considered but is found not persuasive. Those skilled in the art realize that the fact that a method is already described does not preclude undue experimentation. In addition, Applicants quote several publications that were not incorporated by reference in the instant Application.

3. Conclusion

Claims 25 and 26 are allowed or reasons stated in the previous Office Action, paper No. 10, 13, 15.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

[redacted]

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (703) 305-7270. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (703) 308-3804. The fax number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.
Art Unit 1652
Patent examiner

PONNATHAPURA ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER